EXHIBIT 17

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

University of Western Australia,
Junior Party
(Patent 8,455,636,
Inventors: Stephen Donald Wilton, Sue Fletcher and Graham McClorey),

v.

Academisch Ziekenhuis Leiden,
Senior Party
(Application 11/233,495,
Inventors: Garrit-Jan Boudewijn van Ommen, Judith Christina Theodora van Deutekom, Johannes Theodorus den Dunnen and Annemieke Aartsma-Rus).

Patent Interference No. 106,007 (RES)
(Technology Center 1600)

Before: RICHARD E. SCHAFER, SALLY GARDNER LANE, and DEBORAH KATZ, *Administrative Patent Judges*

SCHAFER, *Administrative Patent Judge.*

Decision - Motions - 37 CFR § 41.125(a) (Substitute)

This interference is between University of Western Australia (UWA) Patent 8,455,636 and Academisch Ziekenhuis Leiden (AZL) Application 11/233,495.

I.

The parties have presented the following motions for decision:

(1) UWA Motion 4 to exclude certain AZL evidence. Paper 455

(2) UWA Motion 1 asserting that AZL's claims are unpatentable under 35 U.S.C. § 112(a) because the claims are broader than supported by the written description and/or an enabling disclosure. Paper 210.

(3) UWA Motion 2 asserting that AZL's claims are unpatentable under 35 U.S.C. § 112(b) as indefinite. Paper 211.

(4) UWA Motion 3 seeking the declaration of an additional interference between UWA U.S. Patent No. 8,455,636 AZL Application No. 14/248,279. Paper 212.

(5) AZL Motion 1 asserting that certain of UWA claims are unpatentable over prior art. Paper 181

(6) AZL Motion 2 to deny UWA the accorded benefit date of is Australian Application AU 2004903474. Paper 26.

(7) AZL Motion 3 asserting that certain of UWA's claims are unpatentable under 35 U.S.C. § 101 in view of Association for *Molecular Pathology v. Myriad Genetics, Inc.*, 133 S.Ct. 2107 (2013). Paper 27.

(8) AZL Motion 4 (Responsive) to add two additional claims to its application. Paper 241.

II.

The involved subject matter

The subject matter claimed by the parties relates to "exon skipping." Exon skipping is a molecular biology technique that may be useful for ameliorating or eliminating the effects of certain genetic mutations. Those mutations may result in a shift in the reading frame during protein formation resulting in a non-functional

or partially functional protein. The exon skipping technique, in effect, hides certain pre-mRNA exons from the mRNA formation machinery. As a result, the hidden exon is removed along with introns during the splicing to form mRNA. The exon skipping is said to be caused by the binding of an oligonucleotide that includes a nucleobase sequence that is complementary to a portion of a particular pre-mRNA exon. The complimentary oligonucleotide is referred to as an antisense oligonucleotide or "AON." Both the exon to be discarded and the AON are chosen to restore an open reading frame allowing for the formation of a more complete and more functional protein.

Specifically, the parties' invention is directed to AONs selected to cause skipping of exon 53 of the pre-mRNA associated with the gene responsible for the formation of the protein dystrophin. The absence of dystrophin prevents skeletal muscle development and causes the myopathies of muscular dystrophy. In people suffering from Duchenne muscular dystrophy (DMD), the mutation in the dystrophin gene essentially precludes the formation of any functional dystrophin. By skipping, and thus removing, exon 53 during the formation of mRNA, a reading frame is said to be restored, resulting in the formation of a partially functional dystrophin protein.

III.

UWA Motion 4 to exclude certain testimony

UWA moves to exclude the testimony of Dr. Erik Sontheimer (Exs. 1012, 1067 and 1186) and certain portions of the testimony of Dr. van Deutekom (Ex. 1125). We dismiss the motion.

With respect to Dr. Sontheimer, UWA challenges the admissibility of all three of his declarations on the basis that he is not qualified as an expert in the field under Fed. R. Evid. 702.

The prerequisite to filing a miscellaneous motion to exclude evidence is the timely service of objections to that evidence on the opponent. SO ¶ 151. Objections to evidence must be served within five business days of service of the evidence. 37 C.F.R. § 41.155(b)(1). Where an objection to evidence is served, the proponent of the evidence has ten business days to file supplemental evidence. 37 C.F.R. § 41.155(b)(2). The purpose of supplemental evidence is to allow the proponent an opportunity to cure the alleged evidentiary defect. SO ¶ 155.3. If an objection is not timely made, the objection is waived. SO ¶ 155.1.2. A motion to exclude evidence must identify where in the record the objection was originally made. 37 C.F.R. § 41.155(c); SO ¶ 155.2.2.

AZL filed three declarations by Dr. Sontheimer—Exhibits 1012, 1067 and 1186—on November 18, 2014, December 23, 2014, and February 17, 2015, respectively. As the basis for its motion to exclude, UWA identifies its objections, served February 24, 2015 (Ex. 2150). UWA Motion 4, Paper 455, 1:7-10. UWA never objected to the first and second Sontheimer declarations (Exs. 1012 and 1067). Ex. 2150. Thus, the objections as to those declarations were untimely and considered to have been waived. 37 C.F.R. § 41.155(b)(1); SO ¶ 155.1.2.

With respect to the third Sontheimer declaration (Ex. 1186), the objection on its face appears to have been timely. However, we fail to see why the objection to Dr. Sonetheimer's expertise could not have been made in response to the filing of his first declaration and CV (Ex. 1013). It is apparent from Dr. Sontheimer's cross-examination, that UWA had significant questions as to his expertise that could have formed the basis for a timely objection. The failure to timely give notice of its objections precluded AZL from timely filing supplemental evidence with respect to at least the first two Sontheimer declarations and possibly following a modified course with respect to the third. Under these circumstances, we decline to consider the exclusion of Dr. Sontheimer's third declaration. However, in

evaluating Dr. Sontheimer's testimony, we will consider UWA's arguments on his expertise in evaluating the weight to be give his testimony.

UWA also seeks to exclude ¶¶ 4-18 of Dr. van Deutekom's testimony (Ex. 1125). That testimony is directed to Dr. Sontheimer's credentials. UWA Motion 4, Paper 455, 1:5-6. UWA posits two bases for exclusion: (1) under Fed. R. Evid. 403, the value of her testimony is substantially outweighed by unfair prejudice and needless presentation of cumulative evidence and (2) as hearsay under Fed. R. Evid.. 801 and 802.

With respect to the first basis, the Board is fully capable of weighing any probative value of her testimony against any unduly prejudicial effect. Additionally, her testimony on the point, in light of the extensive record developed in this proceeding, is not so extensive that it is excessively cumulative.

With respect to hearsay challenge, UWA did not raise hearsay as a basis to object to Dr. van Deutekom's testimony in its objections. Ex. 2150. Thus, its objection to admissibility on this ground is considered untimely.

UWA's motion to exclude is dismissed as to Exhibits 1012, 1067 and 1186 and denied with respect paragraphs 4 to 18 of Exhibit 1125.

IV.

UWA Motion 1 - Unpatentability under 35 U.S.C. § 112(a)

A.

UWA Motion 1 argues that AZL's involved claims are unpatentable because AZL's written description is insufficient to support the full scope of subject matter claimed. More specifically, UWA argues that AON "operative sequences are actually highly unpredictable, varying with parameters such as nucleobase sequence, length, backbone chemistry, and internucleotide linkages." UWA Motion 1, Paper 210, 1:14-16. Because we find that, at the time AZL filed its involved application, the sequence length of AONs that would maintain exon

skipping was substantially unpredictable, we hold that AZL's written description did not reasonably convey possession of the full scope of the subject matter of AZL's Claims 15, 76, 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103. We also hold that AZL's sole remaining claim—Claim 77—which is limited to the AON designated h53AON1 having the nucleotide sequence designated by SEQ. ID NO: 29, has not been shown to lack an adequate written description.

1.

AZL's claims are directed to AONs that cause exon 53 skipping during the splicing of human dystrophin pre-mRNA. AZL Clean Copy of Claims, Paper 8. AONs may be said to have two parts—the backbone and the nucleobases. The backbone is the structural framework to which the nucleobases attach. Conventional RNA has a phosphodiester-ribose backbone. Each of AZL's claims require that the AON backbone comprise "a modification selected from the group consisting of" six or seven listed components or classes of components. In other words at least some of the conventional RNA phosphodiester-ribose backbone must be replaced by one or more of the recited components. AZL's claims identify seven possible modifications: 2'-O-methyl, 2'-O-methyl-phosphorothioate (2OMePS), a morpholine ring, a phosphorodiamidate linkage, a modification to increase resistance to RNaseH, a peptide nucleic acid and a locked nucleic acid. *See, e.g.* Claim 78, AZL Clean Copy of Claims, Paper 8, 1:18-2:2.

At the center of AZL's claimed subject matter is the AON whose nucleobase sequence corresponds to AZL's SEQ ID NO: 29 (cuguugccuccgguucug). AZL's disclosure identifies h53AON1 as an AON having that sequence. It also has a 2OMePS backbone. Ex. 1008. 26:14-21. That backbone has two substitutions when compared to the conventional RNA backbone: (1) a phosphorothioate linkage for the phosphodiester linkage and (2) 2'-O-methyl for the 2'-OH of the ribose. h53AON1 is the sole AON identified in AZL's disclosure to cause exon 53

skipping. Ex. 1008, p. 48. That AON is 18 nucleobases in length. Ex. 1008, p. 48, Table 2. The majority of AZL's claims, however, encompass AONs of up to 50 or 80 nucleobases.

We reproduce AZL's Claims 15, 77 and 78 below with paragraphing and bracketed matter added (AZL Clean Copy of Claims, Paper 8):

AZL Claim 15.

An isolated antisense oligonucleotide of
[1] 15 to 80 nucleotides comprising
[a] at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29),
[2] wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA,
[3] said oligonucleotide comprising a modification selected from the group consisting of:
[a] 2'-O–methyl,
[b] 2'-O-methyl-phosphorothioate,
[c] a morpholine ring,
[d] a phosphorodiamidate linkage,
[e] a peptide nucleic acid and
[f] a locked nucleic acid.

AZL Claim 77.

The oligonucleotide of claim 15, wherein the oligonucleotide is
[1] 18 nucleotides and comprises
[a] the base sequence of the sequence cuguugccuccgguucug (SEQ ID NO: 29),
[2] wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA.

AZL Claim 78.

An isolated antisense oligonucleotide of
[1] 18 to 50 nucleotides in length,
[a] wherein said oligonucleotide is
[i] capable of binding to an exon-internal sequence of exon 53 of the human dystrophin pre-mRNA and
[ii] inducing skipping of exon 53, and

[b] wherein h53AON1 (cuguugccuccgguucug) (SEQ ID NO: 29) is capable of binding to said exon-internal sequence of exon 53 pre-mRNA,

[2] said oligonucleotide comprising a modification selected from the group consisting of:

[a] 2'-*O*–methyl,
[b] 2'-*O*-methyl-phosphorothioate,
[c] a morpholine ring,
[d] a phosphorodiamidate linkage,
[e] a modification to increase resistance to RNAseH,
[f] a peptide nucleic acid and
[g] a locked nucleic acid.

AZL Clean Copy of Claims, Paper 8.

2.

To adequately support the claims, the written description "must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (internal quotation marks and brackets omitted). The descriptive text needed varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). "[T]he purpose of the written description requirement is to 'ensure that the scope of the right to exclude, [as set forth in the claims], does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.' " *Ariad* at 1353–54 *quoting Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920 (Fed.Cir.2004)). Thus, the written description plays a vital role in curtailing the permissible claim scope to the actual invention described. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1299 (Fed. Cir. 2014); *Ariad*, 598 F.3d at 1352.

A specification adequately describes an invention when it "reasonably conveys to those skilled in the art that the inventor had possession of the claimed

subject matter as of the filing date." *Ariad*, 598 F.3d at 1351. In other words the written description requirement ensures that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter claimed. *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1255 (Fed. Cir. 2004); *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976). Possession is demonstrated by the disclosure in the specification. *AbbVie*, 759 F.3d at 1299; *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1348 (Fed. Cir. 2011). Determination of possession requires an objective inquiry into the "four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351.

For generic claims, there are a "number of factors for evaluating the adequacy of the disclosure, including 'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue.'" (*AbbVie*, 759 F.3d at 1299); *Capon v. Eshhar*, 418 F.3d. 1349, 1359 (Fed. Cir. 2005). Whether a genus is supported vel non depends upon the nature and breadth of the genus. *Hynix Semiconductor Inc. v. Rambus Inc.*, 645 F.3d 1336, 1352 (Fed. Cir. 2011). Whether the inventors demonstrated sufficient generality to support the scope of some or all of their claims, must be determined claim by claim. *Capon*, 418 F.3d at 1360. "[A] sufficient description of a genus requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1350.

The predictability or unpredictability of the involved science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention. (*Capon*, 418 F.3d at 1360). In the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining

the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. *Capon*, 418 F.3d at 1358; *Enzo Biochem,* 296 F.3d at 1327–28. The appropriate number of exemplified species that one must disclose "necessarily changes with each invention, and it changes with progress in a field." *Ariad*, 598 F.3d at 1351. "If the difference between members of [a species] is such that [a] person skilled in the art would not readily discern that other [species] of the genus would perform similarly to the disclosed members, i.e., if the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus." *Synthes USA, LLC v. Spinal Kinetics, Inc.*, 734 F.3d 1332, 1344 (Fed. Cir. 2013) *quoting Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed.Cir.2004).

An *ipsis verbis* disclosure of a claimed genus is not per se sufficient to meet the written description requirement. *Boston Scientific Corp. v. Johnson & Johnson,* 647 F.3d 1353, 1364 (Fed. Cir 2011); *Enzo Biochem*, 323 F.3d at 968. "[A]n adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries." *Ariad,* 598 F.3d at 1349 (citing *Regents of the University of California v. Eli Lilly and Co.,* 119 F.3d 1559, 1568 (Fed. Circ. 1997)).

3.

UWA argues that at the time AZL's applications were filed, identifying AONs that would result in exon skipping was unpredictable. UWA Motion 1, Paper 210, 4:7 – 9:2. UWA argues that there are many factors that influence the binding of an AON to its target that contribute to the unpredictability. UWA Motion 1, Paper 210, 4:8-10. These are said to include the AON sequence length, accessibility to the target, the appropriate portion of the target, nucleobase sequence, nucleotide mismatches between the AON and target, and modifications to the chemical backbone and internucleotide linkages. UWA Motion 1,

Paper 210, 4:8-10. As a result, according to UWA, each proposed AON must be empirically tested to verify its ability to cause exon skipping. UWA Motion 1, Paper 210, 4:11-13. Because of this unpredictability, UWA argues, AZL's single disclosed operative species within the scope of AZL's claims—the AON designated h53AON1—is insufficient to support the genus of exon 53-skipping AONs encompassed by UZL's claims. UWA Motion 1, Paper 210, 15:18 – 16. In other words UWA argues that from the disclosure of (1) h53AON1, (2) its ability to cause exon 53 skipping, and (3) the rest of the '495 application disclosure, one skilled in the art would not conclude that UZL's inventors had possession of the broad genus of AONs said to be encompassed by AZL's claims.

AZL responds that each of the limitations of its claims is expressly found in its written description. AZL Opposition 1, Paper 392, 6:21 – 7:7. AZL also argues that antisense technology is a mature and predictable field for which AONs are a fundamental tool and that the AON art is sufficiently predictable that the disclosure of the single species h53AON1 in the form a sequence listing provides adequate written descriptive support for the genus claimed. AZL Opposition 1, Paper 392, 2:7-10.

4.

To establish that those skilled in the art considered exon skipping to be unpredictable, UWA relies on the testimony of Dr. Wood. He testifies that exon skipping is unpredictable. Ex. 2081, ¶ 68. In support of his testimony, he identifies a number of publications covering the period 2001 – 2011, a period beginning before and extending after AZL's September 21, 2005, filing date. We summarize some of these publication below.

A 2001 peer-reviewed publication relating to exon 46 skipping titled "Antisense-induced exon skipping restores dystrophin expression in DMD patient

derived muscle cells" (Ex. 2012) indicates that it is difficult to predict the AONs that will bind to the target exon:

> The efficacy of AONs is largely determined by their binding affinity for the target sequence. Due to base composition and pre-mRNA secondary or tertiary structure, *it is difficult to predict which AONs are capable of binding the target sequence*.

Ex. 2012, p. 1548 (emphasis added). The authors tested 12 AONs having overlapping sequences for exon binding and skipping of DMD exon 46 in mouse muscle cells (mAONs 1-12). Ex. 2012, p. 1548. The AONs were complementary to portions of exon 46 differing in specific sequences and sequence length. Ex. 2012, p. 1548, Fig 1B. The mAON's were said to be 15 or 20 nucleobases in length. Ex. 2012, p. 1550, Table 1. Only five of the twelve, mAONs 4, 6, 8, 9, and 11, were identified as binding to Exon 46. Ex. 2012, p. 1548-50, Figs. 1B, 2A and Table 1. Four of the mAONs –4, 6, 9 and 11—were said to cause skipping of exon 46. Ex. 2012, p. 1548 and Figs. 2C and 2D. mAON 8, which was said to bind to exon 46 and shared an eleven nucleotide sequence with mAON 9 and a seven nucleotide sequence with mAON 11, did not cause exon skipping. Ex. 2012, p. 1548. mAON 10 which apparently shared partial nucleotide sequences with mAON 9 and 11 (Fig. 1B), was not reported as binding with exon 46. Ex. 2012, p. 1548. Additional experiments were reported with respect to human muscle cells using the human AON versions (hAONs) said to correspond to mAONs 4, 6, 8, 9 and 11. Ex. 2012, p. 1548-49. The human versions (hAONs) were also 15 or 20 nucleotides in length. Ex. 2012, Table 1. With respect to human muscle cells, hAONs 4, 6, 8 and 9 were said to bind, but only 4, 6 and 8 were said to cause skipping. Ex. 2012, p. 1549. hAONs 9 and 11, which share an eleven and seven nucleotide sequences, respectively, with the exon-skipping hAON 8, were not

identified as causing exon skipping. Ex. 2012, p. 1549. All the exon-skipping AONs were 15 or 20 nucleobases in length.

In a 2002 peer-reviewed article titled "Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy" (Ex. 2010) identified 30 potential AONs for 15 different exons. The authors state that there is no significant correlation between effectiveness and the length or sequence content and that effectiveness of proposed AONs to bind to the desired exon needs to be tested empirically:

> Of the 30 AONs tested, as many as 20 induced specific exon skipping. *There was no significant correlation between the length or sequence content of the AON and its effectiveness (see Table 1)*. We hypothesize that in most cases the mere accessibility of the targeted RNA region, and thus the capability of the AONs to bind, determines their efficacy. The fact that with the AONs tested so far, we have not been able to induce the skipping of exons 45, 47 and 48 would, in this model, be explained by a less accessible configuration of these exons within the secondary structure of the pre-mRNA. To predict the secondary structure of the targeted pre-mRNA regions, we have used the RNA mfold version 3.1 server. Although this analysis hints at the most favorable local structure which may help in the design of AONs, it is not capable of predicting the overall complex structure of the entire DMD pre-mRNA. *We therefore have no insight into the actual position of the targeted sequence within the completely folded RNA structure. Its accessibility, and thus the effectivity of any designed AON, will therefore still have to be tested empirically in the cells, as was done in this study*.

Ex. 2010, p. S76 (emphasis added). The publication appears to rely on much of the same data presented in AZL's involved application. Compare Ex. 2010, Tables 1, 2 and 3 and Figure 1 with AZL's involved application, Ex. 1008, Tables 2, 3 and 4 and Figure 5, respectively. However, unlike AZL's application disclosures, the publication does not make any predictions as to additional AONs that include the

skip-causing sequences, but also include additional exon-complementary nucleobases. All the AONs reported to have successfully caused exon skipping are reported as 15-24 nucleobases in length. Ex. 2010, Table 1.

In another 2002 peer-reviewed publication titled "Improved Antisense Oligonucleotide Induced Exon Skipping in the mdx Mouse Model of Muscular Dystrophy" (Ex. 2017) the authors report making a number of AONs that bound to the region of the dystrophin gene exon 23/intron 23 boundary. Ex. 2017, 646. Three were said to successfully cause skipping. Ex. 2017, p. 631, col. 2. Those AONs were reported to be 17 to 25 nucleobases long.

A 2007 peer-reviewed publication titled "Comparative Analysis of Antisense Oligonucleotide Sequences for Targeted Skipping of Exon 51 During Dystrophin Pre-mRNA Splicing in Human Muscle" (Ex. 2013) notes that rules to assist in determining likely candidates for exon skipping in human and mouse muscle cells *in vitro* had yet to be identified although the sequence length and target region are singled out as important:

> *[S]everal years after the first attempts at dystrophin exon skipping with [AONs], there are still no clear rules to guide investigators in their design, and in mouse and human muscle cells in vitro there is great variability for different targets and exons.* The consensus sequences at the intron–exon boundaries that are involved in splice site selection are only poorly conserved, and the [exonic splicing enhancers] that are involved in exon definition are themselves of multiple motifs and their identification is complex. *Until these key elements are better understood only length and target region seem to be important when designing exon skipping [AONs] for the DMD gene.*

Ex. 2013, p. 807 (citation omitted, emphasis added). The successful AONs tested (A20 and B30) were reported as being 20 and 30 nucleobases in length. Ex. 2013, 803, Table 2.

The 2009 article titled "Guidelines for Antisense Oligonucleotide Design and Insight Into Splice-modulating Mechanisms" (Ex. 2014) notes that notwithstanding the development of various computer programs to assist in identifying AON's as exon skipping candidates, a trial and error procedure was still necessary. The importance of AON sequence length was also noted:

> Each antisense mechanism requires stable and efficient binding of the AON to its target sequence. One obvious determinant of AON efficacy is the accessibility of the target . . . . Several software programs are available to predict the secondary structure of RNA, of which the m-fold server is the most widely used. This server also provides a so-called SS-count for the target sequence, indicating the propensity of a nucleotide to be single stranded in a number of potential secondary structure predictions. This approach probably reflects the actual *in vivo* situation more closely than focusing only on the most energetically stable structure. In addition, the stability and binding energy of the AON to the target sequence influence AON efficiency. *This depends on e.g., AON length and sequence constitution and the free energy of local structures.* To efficiently bind a target sequence, the free energy of the AON-target complex must be higher than that of the target complex and that of the AON. *As AONs are generally only 17–25-nucleotides long, they are unlikely to form stable secondary structures.* However, most AONs can form AON–AON complexes with other AONs of the same sequence (Supplementary Figure S2). The software program RNAstructure 4.5 has a tool that provides the free energy of AON–AON complexes and AON-target complexes, in addition to the free energy of individual AONs and the target sequence. The aforementioned software programs (as well as others) can be used to facilitate AON design (reviewed in ref. 1). *Nonetheless, none of them is 100% conclusive or predictive and in general a trial and error procedure is still involved to identify potent AONs.*

Ex. 2014, p. 548 (emphasis added, citation and footnote omitted).

A 2011 publication titled "Targeted Skipping of Human Dystrophin Exons in Transgenic Mouse Model Systemically for Antisense Drug Development" (Ex. 2015). The authors reported the results of a test using 32 AONs that covered more than two-thirds of human dystrophin exon 50 and its two flanking intron sequences. Ex. 2015, p. 3, paragraph bridging col. 1 and col. 2. The selected AONs had different lengths and were targeted to different portions of exon 50 and its flanking introns. Ex. 2015, Table 1. Thus, all the AONs were antisense to complementary portions of exon 50 and its flanking introns. The results for the 25 AONs with 2OMePS backbones are shown in that publication's Table 1. Ex. 2015, p. 4. Seven of those AONs were identified as causing exon 50 skipping. Review of the Table 1 data shows that the AON length significantly effects exon skipping notwithstanding the inclusion of a common sequence. For example, AONs hE50AO2PS – hE50AO6PS all share the same nineteen base pair sequence. Ex. 2015, Table 1. The 19 and 20 base pair hE50AO2PS and hE50AO3PS were not identified as causing exon skipping. The 22 base pair hE50AO4PS (two additional base pairs) on the 5' end was said to cause skipping in 4% of cells. The 27 base pair hE50AO5PS, with an additional 5 base pairs at the 5' end over hE50AO4PS, was said to cause skipping in 21%. The 32 base pair hE50AO6PS with 5 more base pairs added to the 5' end resulted in 3% notwithstanding that the entire 27 base pair sequence of hE50AO5PS is part of the 32 base pair sequence of hE50AO6PS. We find that this data shows that, given the sequence of an AON capable of causing exon skipping, adding and subtracting additional complementary nucleotides significantly effects the capability of the AON to maintain exon skipping. The data also shows that when an AON's sequence is modified by adding or subtracting a relatively small number of nucleobases, exon skipping is maintained. Compare hE50AO5PS (27 bases) with hE50AO6PS (32

bases) and hE50AO4PS (22 bases). Ex. 2015, Table 1. Additionally, the sequence length of all the exon-skipping AONs fall within the range of 17-32 nucleobases.

The evidence indicates that at the time AZL filed its application, the identification of AONs that will cause exon skipping was generally thought to be unpredictable. One of the significant factors causing that unpredictability is the effect of the number of nucleobases present in the AON.

5.

AZL also argues that once h53AON1 was identified, one skilled in the art would have investigated extended complementary sequences with the expectation that the longer sequences would bind and cause skipping. AZL Opposition 1, Paper 392, 22:2 – 22:9. AZL directs us to Dr. Sontheimer's testimony to support its argument. Dr. Sontheimer testifies that "given the proven exon-skipping ability of h53AON1, one of skill in the art would have a high expectation that such AONs of up to 80 nucleotides in length would bind its target and induce exon skipping." Ex. 1186, ¶ 114, 35:2-5. Dr. Sontheimer does not direct us to any evidence or provide an explanation why one skilled in the art would have had a high expectation. We are not required to credit the unsupported opinions of an expert witness. *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997).

AZL argues that in considering the permissible scope of genus claims with respect to § 112, the consideration is "the predictability of the aspect at issue." AZL Opposition 1, Paper 392, 20:2 – 22:9. AZL cites to *Capon*, 418 F.3d at 1359. AZL argues that none of the publications cited by UWA pertain to the predictability of the "aspect at issue." The aspect at issue is said to be AONs having a sequence capable of binding to and causing skipping of exon 53. AZL Opposition 1, Paper 392, 21: 6-10. According, to AZL the "aspect at issue" is specifically tied to exon 53. AZL Opposition 1, Paper 392, 21:12-16.

The basis of our finding on predictability is not inconsistent with *Capon*. We recognize that h53AON1 and SEQ ID NO:29 are central to AZL's claims. However, we are convinced, based upon the evidence reviewed above, that at the time AZL filed its applications, one skilled in the art would not have predicted that exon 53 skipping would be maintained when the h53AON1 sequence length is extended from 18 nucleobases to 50 or 80 complementary nucleobases as specified in AZL's claims. AZL has not directed us to any publications that would provide a basis for that expectation. AZL's witnesses have not identified any publications or other evidence that supports extending the sequence length to the extent specified in the claims.

AZL argues that the portions of the publications cited by UWA have been taken out of context. AZL Opposition 1, Paper 392, 21: 3-11. We do not agree. We have evaluated the teachings of the complete publications and find that they support Dr. Wood's opinion that exon skipping is unpredictable, at least with respect to the effect of AON sequence length. As we noted above, AZL's witnesses have not directed us to any publications or other evidence that supports their opinions on predictability.

AZL also directs us to test results for AONs of 31, 40 and 50 nucleobases that are said to meet the requirements of AZL's claims and cause exon 53 skipping. AZL Opposition 1, Paper 392, 29:13 – 30:15. The 31 nucleobase AON is UWA's AON having having the nucleobases of its SEQ ID NO:193. AZL Opposition 1, Paper 392, 29:21-23. The tests of the 40 and 50 base AONs were managed and supervised by one of AZL's inventors, Dr. van Deutekom. AZL Opposition 1, Paper 392, 30:1-15.

We fail to be persuaded that these tests show that one skilled in the art would have predicted from h53AON1 as of AZL's September 21, 2005, filing date. UWA's tests were not published until after AZL's filing date. UWA's PCT

application was not published until January 5, 2006. Thus, those skilled in the art would not have had the benefit of UWA's results. Dr. van Deutekom's tests were carried out in December 2014. Ex. 1125, ¶ 52. Thus, Dr. van Deutekom's unpublished *ex parte* tests are of little probity on how the person of ordinary skill in the art would view predictability of exon skipping as of AZL's September 21, 2005, filing date.

AZL sites to the "Written Description Training Materials" of March 28, 2008 (Ex. 1068). According to AZL the PTO has determined, apparently as a matter of undisputable fact, that the AON field is predictable. AZL Opposition 1, Paper 392, 4:6-22. AZL quotes from a portion of the Materials that states that because of the high level of skill, those in the field would consider an applicant to be in the possession of the entire breadth of any claimed genus "that could be predicted from the disclosure" based upon a single species AZL Opposition 1, Paper 392, 4:10-13.

AZL's reliance on the PTO's training materials is misplaced. First, AZL misapprehends the issue. It is not that AON technology in general is unpredictable. The issue is the unpredictability of AONs that will cause exon skipping. Secondly, the training materials presume predictability of the genus AONs from the species. Ex. 1068, p. 44, penultimate paragraph. A presumption of predictability with respect to exon skipping, especially as to altering the sequence length, is simply contrary to the evidence here.

AZL argues once an operative target site is identified, it is straight forward to design longer versions and add additional nucleobases to one or both ends while maintaining complementarity to the pre-mRNA. AZL Opposition 1, Paper 392, 4:15-19. AZL relies on the testimony of Dr. Sontheimer, for support. He testifies:

> A PHOSITA would be able to provide longer sequences simply by starting with the sequence of h53AON1 (SEQ ID NO:29)

> and using its known complementary sequence within the exon 53 pre-mRNA to design and make an oligonucleotide that comprised SEQ ID NO:29 and which contained added bases (either perfectly complementary to its target, or with mismatches) onto either—or both—ends of the SEQ ID NO:29.Thus, according to AZL the design of modified AONs that will cause exon skipping is much more predictable.

Ex. 1186, ¶ 95.

While we agree that those working in the art could easily design and make additional AONs, and likely would investigate additional AONs, by adding complementary bases to h53AON1, Dr. Sontheimer's testimony does not explain why those working in the art would have predicted or expected that adding, for example, 62 complementary nucleobases to h53AON1 for a total of 80 as stated in AZL's Claim 15, would retain the exon skipping ability of h53AON1. The evidence detailed above establishes that those skilled in the art would have expected that adding a small number of nucleobases to an exon skipping AON would retain a degree of exon skipping, but could not predict the effect of adding a significant number of additional bases. Even as late as 2011, a trial and error approach using AONs having sequences that substantially covered the entire exon 50, was used to determine which AONs would cause exon skipping. Ex. 2015, Table 1. For example, Ex. 2015, Table 1 (AONs hE50AO2PS – hE50AO6PS) shows that adding and subtracting nucleobases while maintaining complementarity with the target sequence significantly changed the ability to cause exon skipping even though all the AONs shared the same 19 nucleobase sequence. Ex. 2015, Table 1.. In other words, even the existence of a common structural feature is not sufficient to predict the presence or maintenance of exon skipping.

6.

Looking at the evidence submitted by the parties relating to predictability of exon skipping, we find that one skilled in the art would have appreciated that there

was a substantial degree of unpredictability in changing the sequence length of a known skip-causing AON. We are persuaded that one skilled in the art would not reasonably predict that that AONs of 50 or 80 pre-mRNA exon 53 complementary nucleobases that included the 18 nucleobases of h53AON1 would maintain the exon skipping capability of that AON. Looking to the four corners of AZL's written description, we fail to see an objectively reasonable basis that would permit one skilled in the art to conclude from the single disclosed exon 53-skipping AON, and from the other disclosed AONs said to cause skipping of other exons, that the AZL inventors were in possession of exon 53 skipping AON's having the full range of nucleobases specified in Claims 15, 76, 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103. Because of the unpredictability, AZL's inventors could not have been in possession of the full scope of the subject matter of those claims. We find that AZL's written description, as of its filing date, would not have reasonably conveyed to the person skilled in the art that AZL had possession of the full scope of the AONs having the ranges of nucleobases specified in the claims. We hold that AZL's Claims 15, 76, 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103 are not supported by an adequate written description and are unpatentable under 35 U.S.C. § 112(a).

7.

We come to a different conclusion with respect to AZL's dependent Claim 77. That claim is expressly limited to an AON having the 18 nucleobase sequence represented by SEQ ID NO: 29. While the claim is limited to the specific 18 nucleobase sequence, the claim permits a variation in the modified AON backbone. It lists 5 categories of backbones in addition to 2OMePS. AZL's Clean Copy of Claims, Paper 8,Claims 15 and 77, 1:3-8 and 1:17-17. UWA argues that the variation in the backbone chemistry contributes to the unpredictability of the AONs that will cause exon skipping. UWA Motion 1, Paper 210, 1: 14-16.

UWA directs us to Exhibits 2020 and 2013 and ¶¶ 75 and 77 of Dr. Wood's testimony to establish, *inter alia*, that the choice of backbone effects the degree to which the AONs will cause exon skipping. UWA Motion 1, Paper 210, 5:17 – 7:3.

With respect AZL Claim 77, UWA has not established that one skilled in the art would conclude that AZL's inventors did not have possession of the full scope of the subject matter of Claim 77. The evidence does not establish that the effect of substituting some or all of the 2OMePS backbone of h53AON1 with the other backbone materials recited in the claims renders the effect of the substitution on exon skipping unpredictable. As noted by Dr. Wood:

> 51. In an effort to cope with the many requirements for exon skipping, scientists have explored many different AON chemistries, including AONs with modifications to the nucleobase, the backbone, the internucleotide linkages, and combinations of each.
>
> 52. AON chemistries can vary significantly from naturally occurring nucleotides. However, they preserve the ability to form Watson-Crick base pairs with pre-mRNA through the maintenance of nucleobases (sometimes modified) in the correct spatial conformation.

Ex, 2081, ¶¶ 51-52. Dr. Wood then discusses a number of known substitute backbones, explaining the effect of each on the properties of the AON. Ex. 2081, ¶¶ 52-60. AZL's Dr. Sontheimer similarly testifies that the effect of the backbones on the AONs was known at the time the AZL's '495 application was filed. Ex. 1186, ¶¶ 119-124. While the record shows modifying the 2OMePS backbone of h53AON1 would likely change the efficiency, i.e., the degree of skipping, we are not convinced that the expected change in efficiency on h53AON1 is sufficient to hold that the changes are so unpredictable that AZL's inventors were not in possession of the full scope of the subject matter of Claim 77. As noted by Dr. Wood, the changes in the chemistry "preserve[s] the ability to form Watson-

Crick base pairs with pre-mRNA through the maintenance of nucleobases (sometimes modified) in the correct spatial conformation. " Ex. 2081, ¶ 20:52. His testimony is consistent with Ex. 2020 that teaches that differences in skipping efficiency between AONs with different backbones appear to be sequence and not chemistry (i.e., backbone) dependent, although certain backbones may be less sequence dependent than others:

> [D]ifferences in efficiency between PMO and 20MePS appear to be sequence and not chemistry dependent. Finally, the results indicate that PMOs may be less sequence specific than 20MePS.

Ex. 2020, p. 257 (Conclusions).

UWA has failed to meet its burden to show that the subject matter of the full scope of Claim 77 was not in the possession of AZL's inventors and lack written descriptive support.

B.

UWA argues that AZL's application fails to enable one skilled to make and use the full scope of the claimed invention. UWA Motion 1, Paper 210, 24:12-13. UWA bases its argument on the scope of UWA's claims, the unpredictability of exon skipping, the amount and nature of experimentation necessary and the lack of clinical data to establish therapeutically useful AONs. UWA Motion 1, Paper 210, 25:21 – 30:21. We held above that there is a significant degree of unpredictability with respect to exon skipping, at least with respect to AON sequence length.

UWA says that undue experimentation is required due primarily to unpredictability and the very large number and variety of potential AONs covered by the claims that would need to be tested. UWA Motion 1, Paper 210, 28:1 – 30:3. Making and testing even a small number of possible AONs, says UWA, requires a massive investment in time and effort. UWA Motion 1, Paper 210, 28:19 – 29:4.

1.

UWA again relies on Dr. Wood's testimony. He testifies that due to the unpredictability of exon skipping, and due to the potential mismatches between the AON and pre-mRNA, different possible backbones, and sequence length of the AONs, a very large number of AONs is potentially covered by the claims. He presents a calculation of the number of possible AONs covered by the claims. Ex. 2081, ¶ 192. He further testifies that a large number of potentially covered AONs would need to be synthesized and tested. Ex. 2081, ¶ 422. As a result a massive amount time and effort would be necessary to perform this testing. Ex. 2081, ¶ 423.

AZL argues that the person of ordinary skill in the art would have been able to readily make the AONs "recited in the '495 application." AZL Opposition 1, Paper 392, 12:20-21. It further argues that in light of the high level of skill in the art, the public availability of the sequence of exon 53, the examples in AZL's specification of the effectiveness of the 2OMePS AONs, a person of ordinary skill "would have been capable of using the [AONs] of the '495 claims to induce exon [53 skipping.]" AZL Opposition 1, Paper 392, 14:3-8. With respect to the amount of experimentation, AZL argues that a reasonable amount of routine experiment does not violate the enablement requirement and having disclosed the sequence of h53AON1, only routine testing was necessary to see if exon skipping was induced. AZL Opposition 1, Paper 392, 14: 23 – 16:13.

While we view UWA's computation of the number AONs covered by the claims (Ex. 2081. ¶¶ 191-195) to be overly speculative, AZL does not appear to challenge that its claims encompass an extremely large number of possible AONs. We are persuaded that a very large number of AONs would need to be synthesized and tested for exon skipping activity and would amount to undue experimentation.

Undue experimentation is a matter of degree. *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). While necessary testing may be routine, even routine testing may be undue if it involves synthesizing and testing a very large number of candidates. *Wyeth and Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1385-86 (Fed. Cir. 2013).

While routine experimentation, even if difficult and time consuming, does not mandate a conclusion that the amount of experimentation is undue *(Falkner v. Inglis*, 448 F3d 1357, 1365 (Fed. Cir. 2006)), we view this case to be very similar to *Wyeth and Cordis*. There the claims were directed to a treatment for preventing restenosis using a class of compounds called rapamycin. Rampamycins include a specific macrocyclic triene ring. The patents involved disclosed a single rapamycin compound which included a specific substituent at one location of the ring. The evidence showed that because of the large number of possible modifications at the substituent site on the ring there were a very large number of potential candidate rapamycins. Each potential rapamycin would need to be tested to see if it prevented restenosis. The court held that the amount of testing under these facts indicated a degree of experimentation that was undue. Similarly, the record here, shows that exon skipping has a significant degree of unpredictability and that it is uncontested that there are a very large number of possible AONs within the scope of AZL's claims and a very large number of AONs would need to be manufactured and tested to determine whether exon skipping capability was present. In our view because of the unpredictability of exon skipping, and the large number of potential candidate AONs within the scope of the claims, an undue amount of experimentation would be required to practice the full scope of AZL Claims 15, 76. 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103. Those claims are unpatentable under 35 U.S.C. § 112(a).

2.

We again reach a different conclusion with respect to Claim 77. As we noted above, this claim is much more limited in its scope. It is limited to the specific 18 nucleobase sequence of SEQ ID NO: 29. While the specific backbone may be varied, the evidence discussed above with respect to the written description shows that those working in the art were aware of the effects of modifying the backbone.

UWA has not established that an undue amount of experimentation would have been necessary to make and test AONs having the 18 nucleobase sequence of SEQ ID NO: 29 with the different backbones recited Claim 77. UWA has failed to meet its burden of establishing that AZL's Claim 77 is not enabled for its full scope.

C.

UWA motion 1 is granted with respect to Claims 15, 76, 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103, but denied with respect to Claim 77.

V.

UWA Motion 2 – Unpatentability under 35 U.S.C. § 112(b)

A.

UWA "requests entry of judgment that [AZL's] involved Claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, 100-103 in Application No. 11/233,495 . . . are indefinite and therefore unpatentable under 35 U.S.C. § 112(b)." UWA Motion 2, Paper 211, 1: 2-5. UWA argues that the claims do not inform a person of ordinary skill in the art of the level of skipping, the conditions for testing skipping, and how to measure or evaluate exon skipping. According to UWA, different techniques can be used to measure exon skipping. An AON might meet the claim requirements when considered by one technique while in another it would not, thus resulting in indefinite claims:

> [A]pplying a broad interpretation of the claims where any means of measuring exon skipping is permitted, some AONs *may* fall within the scope of the "comprising" claims, but when exon skipping is measured in another way, they *may* not. This is the essence of ambiguity.

UWA Motion 2, Paper 211, 17: 7-9 (emphasis added). As a result, UWA says, AZL's claims are indefinite under *Honeywell Int'l, Inc. v. ITC*, 341 F.3d 1332 (Fed. Cir. 2003). More specifically, UWA argues that the claims and specification do not provide guidance on how to determine if exon skipping was induced or how exon skipping is to be measured or detected. UWA Motion 2, Paper 211, 19:4 – 20:18

B.

The Supreme Court has explained the definiteness requirements of § 112 in *Nautilus, Inc. v. Biosig Instruments, Inc.*, ___ U.S. ___, 134 S. Ct. 2120, 2129 (2014).

> [W]e read § 112, ¶ 2 to require that a patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty. The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable. The standard we adopt accords with opinions of this Court stating that "the certainty which the law requires in patents is not greater than is reasonable, having regard to their subject-matter." *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270, 37 S.Ct. 82, 61 L.Ed. 286 (1916).

134 S. Ct. at 2129. UWA, who bears the burden of proof (37 CFR § 41.208(b)), must therefore establish that AZL's claims do not inform those skilled in the art of the scope of the claims with "reasonable certainty."

C.

With respect to Claims 15, 76, 80, 82, 84, 86, 88-90, 98, 101, and 102 UWA directs us to Dr. Wood's testimony. He testifies that AZL's claims encompass a

very large number of possible AONs and that exon skipping is unpredictable. Ex, 2081, ¶¶ 455-457. He also testifies that under different testing conditions, an AON "might" be identified as causing exon skipping under one set of condition but it "might" not be identified under different conditions:

> When exon skipping is measured under one set of conditions an AON meeting the structural features of the claims might be found to meet the structural requirement of inducing skipping, but when measured under another set of conditions it may not.

Ex. 2081, ¶ 458.

D.

We are not convinced by UWA's arguments and evidence.

1.

We do not think that *Honeywell* is applicable under the facts here. In *Honeywell*, the claims required a specific numerical range for "melting point elevation" (MPE). The evidence showed that depending on the specific way MPE was tested, the same sample would either be within or outside the specified range. *Honeywell*, 341 F.3d at 1336. The court held that the Honeywell's claims, which did not identify the method of testing MPE, were indefinite with respect to the method of how the product was to be tested. *Honeywell*, 341 F.3d at 1340. Unlike the claims involved in *Honeywell*, AZL's claims do not require any specific degree of exon skipping. They only require that the AONs cause, or are capable of causing, some amount of exon skipping. Thus, any degree of skipping will bring the AON within the scope of the skipping requirement of the claims. This fact alone distinguishes AZL's claims from those involved in *Honeywell*. Additionally, unlike *Honeywell*, UWA has not directed us to evidence establishing that different tests would in fact lead to different results for the same AON.

2.

Additionally, while Dr. Wood testifies to the possibility of variability in results for different tests, we have not been directed to evidence sufficient to establish that one having ordinary skill in the art would not be able to determine whether an AON caused exon 53 skipping notwithstanding the variability in the results of different tests. The level of skill in the art is very high. As stated by Dr. Wood:

> A person of ordinary skill in the art would have a Ph.D. degree in cell biology, genetics, molecular biology, or an equivalent, and several years of experience with AONs for inducing exon skipping, including familiarity with *in vitro* and *in vivo* methods for testing the safety and efficacy of such AONs. Further, a person of ordinary skill in this art would have at least some knowledge of, and experience with, chemical modifications that may be incorporated into AONs, such as modifications to the backbone and/or nucleobases of the AONs, and the impact of those modifications on the utility of the AONs. The person of ordinary skill in the art would also have at least some understanding of the use of AONs for inducing exon skipping in the context of medical conditions, such as DMD, that may be treated by administering such AONs.

Ex. 2081, ¶ 179. Those working in this field are aware of an array of different tests to determine exon skipping. Ex. 1008, 24:4 – 26:6. The evidence does not establish that those highly skilled scientists are not aware of the limitations and the appropriate use of each of these routinely used tests and would not be able to accurately assess whether exon skipping was actually present or not.

Additionally, we note that, at least where standardized protocols were used, the different tests reliably show comparable results:

> Results from the different laboratories were highly concordant with minimal inter- and intralaboratory variability, particularly with quantitative immunohistochemistry. There was a good level of agreement between data generated by

> immunohistochemistry and Western blotting, although immunohistochemistry was more sensitive. Furthermore, mean dystrophin levels determined by alternative quantitative immunohistochemistry methods were highly comparable.

Ex. 2028, p. 1. Thus, notwithstanding variability in test results, it appears one skilled in the art would still reliably determine whether or not an AON induced exon skipping.

The evidence here fails to establish that the variability in the results of different tests would result in those skilled in the art being unable to reasonably determine whether and AON meet the claim requirement of "inducing exon skipping." Claims 15, 76, 80, 82, 84, 86, 88-90, 98, 101, and 102 have not been shown to be indefinite.

E.

UWA also argues that the phrase "capable of binding to an exon-internal sequence of exon 53" used in Claims 78, 79, 82, 84, 86, 88-90, 97, 98, and 100-103 renders those claims indefinite. UWA Motion 2, Paper 211, 21:15 – 25:20. Relying on the same arguments it made with respect to detecting exon skipping, UWA says the "capable of binding" is indefinite because the claims "fail to recite the conditions for testing, detecting and evaluating exon skipping." UWA Motion 2, Paper 211, 22:5-8. We held above that UWA's argument with respect to "inducing exon skipping" was unpersuasive. In view of the high level of skill in the art, we are not convinced that one skilled in the art could not reasonably evaluate whether an AON is capable of binding to exon 53 for the reasons stated above with respect to detecting exon skipping.

Additionally, we note that, "capable of binding" and its equivalent "capable of hybridizing" are ubiquitously used in the involved technology. Indeed, both parties use the phrases in their respective written descriptions to describe the invention. For example, UWA says: "The present invention describes antisense

molecules capable of binding to specified dystrophin pre-mRNA targets and re-directing processing of that gene." Ex. 2046, 23:27-29. AZL similarly teaches: "An oligonucleotide capable of hybridizing to pre-mRNA at a location of an exon that is normally included in the mature mRNA can direct the exclusion of the thus targeted exon or a part thereof." Ex. 1008, 1:27-29. The evidence to which we have been directed is insufficient to establish that those working in the art would not understand these often used phrases as they are used in the context of AZL's specification.

F.

UWA also argues that because "exon-internal sequence" is undefined, Claims 78, 79, 82, 84, 86, 88-90, 97, 98, and 100-103 which include that phrase are indefinite. UWA Motion 2, Paper 211, 22:9 – 23:18. UWA's Dr. Wood testifies that the AZL's applications do not provide any guidance on the meaning of the phrase. Ex. 2081, ¶ 209. AZL says "internal means 'within' the exon, which also means located between the ends of exon 53 . . . ." Paper 396, 9:4-6. AZL's, Dr. Erik Sontheimer, testifies that an exon-internal sequence "does not include an exon/intron boundary or an intronic sequence . . . ." Ex. 1067, ¶ 17.

While AZL's specification does not appear to define the phrase, UWA does not explain why the phrase needs definition. The phrase must be considered in the context of the claim in which it appears (*IGT v. Bally Gaming Int'l, Inc.*, 659 F.3d 1109, 1117 (Fed. Cir. 2011)) and of the specification of which it is apart (*Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed.Cir.2005) *(en banc)*. The literal meaning of the words, as used in the phrase "exon-internal sequence of exon 53" specifies a sequence that is inside of, or in the interior portion of, exon 53. AZL's construction is consistent with the literal meaning of the phrase in the context of the claim. UWA has not directed us to sufficient evidence that those working in the art would understand the phrase in a manner different than its literal meaning

of the words when read in the context of the claim and the rest of the specification. Nor has UWA provided a basis as to why the phrase should be given a connotation different than the literal meaning. We construe "exon internal sequence" to mean a sequence that is inside the exon but excludes that two bounding nucleobases at the 3' and 5' ends of the 212 nucleobase exon 53. In other words, the exon internal sequence is 210 nucleobase sequence of exon 53 but excluding its ending 5' and 3' nucleobases.

UWA has failed to show that the phrase "exon-internal sequence" is not clear and does not inform one skilled in the art of the scope of the claims with reasonable certainty.

G.

UWA also argues that Claims 78, 79, 82, 84, 86, 88-90, 97, 98, 100 and 103 are indefinite because these claims require that the AONs must be capable of binding to an exon-internal sequence of exon 53 to which h53AON1 is also capable of binding. The claims are said to be indefinite because

> no conditions are specified in the claims, the application, or the file history, for determining whether h53AON1 is capable of binding to the "exon-internal sequence' sequence" that is bound by the claimed AON. (Exh. 2081 at ¶ 449.) Also, there is no disclosure in the AZL applications concerning how "binding" of the AON to the "exon-internal sequence" of the pre-mRNA is assayed or measured. (Exh. 2081 at ¶ 446.) The AZL applications do not describe how to reach a conclusion that the AON has bound, other than by reference to the separate and distinct functional requirement recited in claims that exon skipping is induced. (Exh. 2081 at ¶ 449.) Nor does the intrinsic evidence inform a person of ordinary skill in the art whether the same conditions for binding of the claimed AON and h53AON1 are required, or if different conditions may be used. (Exh. 2081 at ¶ 449.) This might be expected as "binding" is never directly measured in the AZL applications.

UWA Motion 2, Paper 211, 23:22 – 24:9. UWA again relies on Dr. Wood's testimony for support. He testifies that binding of nucleic acids is "exquisitely" sensitive to the conditions employed and there is no way to know if binding occurs because the conditions are not specified. Ex. 2081, ¶ 247.

We do not credit Dr. Wood's testimony on this point. His referenced testimony does not direct us to evidence in support. We are not required to credit unsupported expert testimony. *Rohm and Haas*, 127 F.3d 1089, 1092 (Fed. Circ. 1997). *See also, Phillips v. AWH Corp.*, 415 F.3d at 1318 ("[C]onclusory, unsupported assertions by experts as to the definition of a claim term are not useful . . . .") and *Aristocrat Techs. Austl. PTY Ltd. v. Int'l Game Tech.*, 709 F.3d 1348, 1360-61 (Fed. Cir. 2013) (an explanation of only "how" a person of ordinary skill would understand a claim term without an explanation of "why" is "not useful" and should be discounted). Dr. Wood does not direct us to sufficient evidence supporting his testimony that the conditions of binding in either the claims or the specification are necessary. As we noted above, the level of ordinary skill in the art is very high. Based on the evidence to which we have been directed, we fail to see that those working in the art would not use routine testing and conditions to perform the necessary comparison between the AON and h53AON1. The fact that some experimentation may be necessary to determine whether an AON falls within the scope of the claims does not render the claims indefinite. *Exxon Research and Engineering Co. v. U.S.*, 265 F.3d 1371, 1379 (Fed. Cir. 2001); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557 (Fed.Cir.1983).

G.

UWA has failed to satisfy its burden of establishing that AZL's Claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, 100-103 fail to inform persons skilled in the art of the scope of the claims with reasonable certainty. Accordingly, those claims have not been shown to be indefinite under 35 U.S.C. 112(a).

VI.

UWA motion for the declaration of an additional interference

UWA moves for the declaration of an additional interference between its currently involved patent, 8,455,636, and another AZL application, 14/248,279. The '279 application is said to be a continuation of AZL's involved '459 application. Because UWA has not established that it has a basis upon which it could prevail on priority, we deny the motion.

A.

The Claims of the ''279 application are directed to a method of inducing exon 53 skipping, an expression vector encoding a transcript comprising an AON capable of binding to exon 53 and a gene delivery vehicle comprising that vector. Like AZL's involved claims in this interference, the subject matter of the '279 application claims centers on SEQ. ID. NO: 29 and the AON designated h53AON1. Ex. 2053, pp. 2-4.

B.

A party in an interference may suggest the declaration of an additional interference:

> A party may suggest . . . the declaration of an additional interference. The suggestion should make the showings required under § 41.202(a) of this part.

37 CFR § 41.203(d). Section 41.202(a) provides in relevant part:

> An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must: . . . (4) Explain in detail why the applicant *will prevail on priority* . . . .

37 C.F.R. § 41.202(a) (emphasis added). Paragraph (e) of § 41.202, further requires:

> (e) Sufficiency of showing. (1) A showing of priority under this section is not sufficient unless it would, if unrebutted, support a determination of priority in favor of the party making the showing.

37 C.F.R. § 41.202(e). Priority may be established by showing an earlier reduction to practice, or an earlier conception coupled with diligence to a later reduction to practice. 35 U.S.C. § 102(g) (2011). The reduction to practice may be constructive or actual. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998).

The mechanism for suggesting an additional interference is a miscellaneous motion. Standing Order, Paper 2, ¶ 203.1. As noted in the Standing Order: "The motion must comply with the requirements of [37 C.F.R. § 41.]202(a) *even for a patent*." *Id* (emphasis added). The party filing a motion has the burden of proof. 37 CFR §§ 41.121 (b) and 41.208(b).

C.

UWA argues that "[s]ince all of the AZL claims are unpatentable for a lack of written description and enablement, priority is not an issue." UWA Motion 3, Paper 212, 7:4-5. UWA also argues that

> the AZL '279 application, the AZL '495 application and the AZL PCT application from which the AZL '279 application claims benefit, do not adequately describe or enable the claims in the AZL '279 application. As such, AZL is not entitled to a filing date earlier than its April 8, 2014 filing date. (Ex. 2081, ¶¶279-433). As such, UWA will prevail in the interference.

UWA Motion 3, Paper 212, 7:10-14. Raising essentially the same arguments that it raised with respect to its Motion 1 (Paper 210), UWA argues that the claims of AZL's '279 application are unpatentable under 35 U.S.C. § 112 for failing to meet the written description and enablement *for the full scope* of the claimed subject matter. UWA Motion 3, Paper 212, 12:8 – 15:5. UWA premises its argument on the assertion that AZL's '279 application and its parent applications "disclose just

a single species of AON allegedly capable of inducing *in vitro* skipping of exon 53 . . . ." UWA Motion 3, Paper 212, 13:6-8 and 14:9-12. UWA does not assert that that the "single species" is not adequately disclosed in those applications or does not meet the limitations of Proposed Count 2.

D.

UWA's Motion 3, does not attempt to show an earlier actual reduction to practice or an earlier conception coupled with diligence. Rather, it argues that each of its earlier applications is a constructive reduction to practice of the subject matter of Proposed Count 2 entitling it to an effective filing date of June 28, 2005. UWA Motion 3, Paper 212, 6:16 - 7: 9. On the other hand, argues UWA, AZL is not entitled to a date earlier than the April 8, 2014, filing date of the '279 application. UWA Motion 3, Paper 212, 7: 10-14. The reason, according to UWA, is that

> the AZL '279 application, the AZL '495 application and the AZL PCT application from which the AZL '279 application claims benefit, do not provide written description or enablement for the claims in the AZL '279 application.

AZL's claims are said not to be supported for the "full scope" of the subject matter claimed. UWA Motion 3, Paper 212, 12:8 – 15:5.

Assuming that UWA is correct about the unpatentability of AZL's '279 claims under 35 U.S.C. § 112(a) due to the lack of support for the full scope in '279 application and in UWA's parent applications, AZL has failed to establish that it will prevail on priority. 37 C.F.R. §§ 41.203(d), 42.202(a), 41.202(e); SO ¶ 03.1.

UWA notes that AZL's '279 application claims benefit of AZL's '495 application (involved herein) and PCT application PCT/NL2003/000214 filed March 21, 2003. Those applications are said to "disclose just a single species of AON allegedly capable of inducing *in vitro* skipping of exon 53 . . . ." UWA

Motion 3, Paper 212, 13:6-8 and 14:9-12. UWA does not allege that the disclosures of that single species (h53AON1) in the '279 application and AZL's earlier applications, in the context of the specifications of those applications, does not provide a written description and enabling disclosure of an embodiment meeting the limitations of UWA's Proposed Count 2.[1] Thus, UWA's has not shown the '279 application and each of its parent applications, is not a constructive reduction to practice of an embodiment meeting the limitations of the proposed count.[2] For the purpose of priority in an interference, where a "parent application is relied upon as a prior constructive reduction to practice[,] . . . the § 112, first paragraph requirements need only be met for an *embodiment* within the count." *Hunt v. Treppschuh*, 523 F.2d 1386, 1389 (CCPA 1975). *See also*, *Falkner v. Inglis*, 448 F.3d 1357, 1362 (Fed. Cir. 2006). UWA's earliest claimed benefit application is AU 2004 903474, filed June 28, 2004, a date subsequent to AZL's earliest possible constructive reduction to practice (PCT application PCT/NL2003/000214 filed March 21, 2003). UWA has not provided argument nor directed us to evidence sufficient to establish a reasonable basis upon which it will prevail on priority.

A junior party seeking an interference may have a basis to assert that an opponent's claimed subject matter is not patentable. However, without a colorable basis for a junior party to prevail on priority, there is simply an inadequate foundation to invoke the Board's interference jurisdiction to address patentability. Allegations of unpatentability, on their own, do not provide an adequate justification for the Office to exercise discretion to allow an interference to proceed

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[1] Proposed Count 2 is set out in Appendix A to UWA's motion (Paper 212).
[2] When this interference was declared AZL was accorded the benefit of the filing dates of its earlier application back to its PCT application PCT/NL2003/000214 filed March 21, 2003.

solely to address patentability issues. *See* 35 U.S.C. § 135(b) (2010) ("The Board of Patent Appeals and Interferences shall determine questions of priority of the inventions and may determine questions of patentability.")

E.

UWA's Motion 3 requesting an additional interference between Patent 8,455,636 and AZL Application 14/248,279 is denied.

VII.

AZL's motion for unpatentability over prior art

AZL moves for a judgment that UWA's involved claims are unpatentable on the following grounds:

1. Claims 1–12, 14–16, 19–29, 31–33, 37 and 38 under 35 U.S.C. § 102(e) or § 103(a) over International Published Application WO2004/0834321 ("VO"), relying additionally on two Koenig et al publications (collectively Koenig) as evidence supporting anticipation or to establish obviousness;
2. Claims 16–18 and 33–35 under § 103(a) as unpatentable over the combined teachings of VO, Koenig and International Published Application WO 2001/72765 (Bennett).
3. Claims 13 and 30 under § 103(a) over the combined teachings of VO, K1, K2 and WO 1994/26887 (Kole);
4. Claims 36 and 39–43 under § 103(a) over the combined teachings of VO, Koenig and WO 00/15780 (Latchman).

A.

UWA Claims 1, 4, 19 and 20

UWA's involved Claim 1 is directed to an AON of 20-50 nucleobases that hybridizes to a region of exon 53 of the human dystrophin gene causing exon 53 to be skipped. The AON must include at least 20 consecutive nucleobases of UWA's

SEQ ID NO: 193. Additionally, the uracil bases may be substituted with thymine. We reproduce UWA's Claim 1 below with paragraphing added:

> 1. An isolated antisense oligonucleotide
>
> of 20 to 50 nucleotides in length comprising
> at least 20 consecutive nucleotides of SEQ ID NO:193,
> wherein the oligonucleotide specifically hybridizes to an exon
> 53 target region of the human dystrophin gene
> inducing exon 53 skipping, and
> wherein the uracil bases are optionally thymine bases

UWA Clean Copy of Claims, Paper 12, App A-1, Claim 1. SEQ ID NO:193 also has the following 31 nucleobase sequence:

CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G

Ex. 1003, Table 1A, col. 17; Table 3A, 56:52-54. That sequence is also designated by its annealing site H53A(+39 + 69). *Id.* UWA's other independent claim, Claim 19, is essentially identical to Claim 1 except that it identifies the sequence by the annealing site H53A(+39 + 69) rather than referring to SEQ ID NO:193. UWA Clean Copy of Claims, Paper 12, App A-3, Claim 19. Claims 2 and 20 limit the AONs to 20 to 31 nucleotides. UWA Clean Copy of Claims, Paper 12, App A-3, Claims 2 and 20.

1.

AZL relies on International Published Application WO2004/0834321 ("VO"). It is of record as Ex. 1007. Its status as prior art to UWA's claimed subject matter is not challenged. VO is the published version of the specification of AZL's International Application PCT/NL03/000214. Ex. 1007, p. 1. AZL's involved application claims to be a continuation of that international application.

AZL principally relies on VO's disclosure of h53AON1. As we discussed above, that AON is described as having an eighteen nucleobase sequence and said to cause exon skipping of exon 53. Ex. 1007, Table 2, 48:33. UWA's SEQ ID

NO: 193 is a 31 nucleobase sequence that includes the 18 bases of h53AON1. Ex. 1003, Table 3A, 56:52-54. We compare the sequences below with the identical portions shown in bold:

SEQ ID 193 (31mer): cauuc aa**cug uugcc uccgg uucug** aaggx g
VO (h53AON1 18mer): **cug uugcc uccgg uucug**

One difference between h53AON1 as described in VO differs from the AON of UWA's Claim 1 and 19 is the number of nucleobases. h53AON1 has 18. UWA's Claims 1 and 19 require at least 20 consecutive nucleobases of SEQ ID NO:193 or of annealing site H53A(+39+69). VO also teaches that the AONs are "preferably complementary to a consecutive part of between 16 and 50 nucleotides of said exon RNA." Ex. 1007, 9:28-30. It is uncontested that the Koenig references (Exs 1010 and 1011) teach the complete sequence of exon 53 was known to those working in the art. Given h53AON1, AZL argues, it would have been obvious to make AONs having different lengths that included the sequence of h53AON1 but still complementary to exon 53. The person having ordinary skill in the art would have been motivated to investigate AONs of different lengths in order to determine the optimum length for exon skipping. Ex. 1012, ¶ 56. Thus, according to AZL, UWA's Claims 1, 4, 19 and 20 encompass subject matter that would have been obvious and are unpatentable under 35 U.S.C. § 103(a)

UWA argues that there is no rationale provided in the combined teachings of the references to modify h53AON1 to produce an AON within the scope of UWA's claims. UWA Opposition 1, Paper 393, 22:19-22. UWA also argues that because of the unpredictability of exon skipping there would be no reasonable expectation of success in making any modifications. *Id.* at 22:21-23.

2.

VO specifically teaches that AONs are "preferably complementary to a consecutive part of between 16 and 50 nucleotides of said exon RNA." Ex. 1007,

9:28-30. In our view, that language at least suggests to one having ordinary skill in the art to modifying an AON that has been disclosed to cause exon skipping by changing its sequence length by adding additional exon 53 pre-mRNA nucleobases.

We find no merit in UWA's argument that VO's method of generating AONs does not include taking a known exon-skipping AON and adding nucleobases to it. UWA Opposition 1, 23:79-23. First, we read VO's disclosure to teach making complementary AONs of various lengths:

> The complementary regions are preferably designed such that, when combined, they are specific for the exon in the pre-mRNA. Such specificity may be created with various lengths of complementary regions as this depends on the actual sequencesin other (pre-)mRNA in the system.

Ex. 1007, 3:12-17. Secondly, regardless of the presence or absence of an express teaching in VO, one skilled in the art would have been motivated to modify the sequence length of AONs to determine the optimum length for causing exon skipping. Ex. 1012, ¶ 56.

UWA also argues that because of unpredictability of exon skipping there would be no reasonable expectation of success in modifying the AONs length. We recognize, as we detailed above, that there is a significant degree of unpredictability in the effect of AON sequence length on the ability and efficiency of an AON to cause exon skipping. However, those working in the art were also aware that a degree of exon skipping capability would likely be maintained due to a change in a small number of complementary nucleobases of an AON known to cause skipping. As shown in Exhibit 2012, AONs hAON4 and hAON6, each are taught to cause exon skipping. Ex. 2012, p. 1549, first column. hAON4 was fifteen nucleobases long. hAON6 included the same fifteen bases but five additional bases to the 5' end. Ex. 2012, Table 1. Thus, notwithstanding the

unpredictability, one having ordinary skill in the art would have had a reasonable expectation of success that exon skipping would be maintained when a small number of complementary nucleobases are added to h53AON1. It would have been obvious, for example, to add the two complementary nucleobases dictated by the known sequence of exon 53 to either end of h53AON1 with a reasonable expectation that the resultant 20 base AON would cause exon skipping. See VO, Ex. 1007, 9:28-30 (the AONs are preferably complementary to a consecutive part of between 16 and 50 nucleotides of the exon RNA). Thus, Claims 1, 4, 19 and 20 are unpatentable under 35 U.S.C. § 103.

B.

UWA Claims 5-18, 21-37, 41 and 43

These claims depend, directly or indirectly from Claims 1 and 19. AZL argues that the additional limitations of these claims do not present patentable distinctions over Claims 1 and 19. AZL Motion 1, Paper 181, 15:25 – 27:10.

AZL identifies where the additional limitations are taught in VO, Kole, Bennett or Latchman. *Id.* We have reviewed the teachings of these references and concur that the additional limitations of Claims 5-18, 21-37, 41 and 43 are taught in either VO or the other references and do not present patentable distinctions over the citied art. UWA's opposition neither challenges that the references teach the additional limitations nor that the add limitations present features that would themselves render the subject matter of these claims nonobvious. UWA Opposition 1, Paper 393, 28:5-13.

Claims 5-18, 21-37, 41 and 43 are unpatentable under 35 U.S.C. § 103(a).

C.

UWA Claims 2, 3, 38-40, and 42.

These claims depend from Claim 1. They require an AON "comprising SEQ ID NO: 193" or "consisting of SEQ ID NO: 193." Those AONs must also

"specifically hybridize[] to an exon 53 target region of the human dystrophin gene inducing exon 53 skipping." UWA Clean copy of Claims, Paper 12, Claim 1. Thus these claims specify AONs that include at least the full 31 nucleobase sequence of SEQ ID NO: 193.

1.

AZL argues that Claims 2 and 3 are anticipated by VO when considered with the Koenig disclosures which disclose, *inter ali*a, the full sequence of Exon 53. AZL Motion 1, Paper 181, 3:17-4:6.

While we agree that one skilled in the art following VO's teachings could manufacture all the possible AONs that include the sequence of AZL's SEQ ID NO:29 and would be complementary to exon 53, we are not persuaded that one skilled in the art would have a basis to reasonably expect that UWA's minimum 31 nucleobase AONs would cause exon skipping. We held above that there is a substantial degree of unpredictability in the exon skipping art especially with respect of AON sequence length. When given the sequence of an AON which will cause exon skipping, in this case the AON having the sequence of AZL's SEQ ID NO: 29, one skilled in the art would reasonably have expected that modifying that sequence by adding or subtracting a relatively small number of exon 53 complementary nucleobases would likely maintain exon skipping. However, AZL's h53AON1 differs from UWA's SEQ ID NO: 193 by thirteen nucleobases. Because of the unpredictability of the effect of changing the AON sequence length on exon skipping, we are not persuaded that VO's teaching of h53AON1 would put one having ordinary skill in the art in possession of the exon skipping AONs of Claims 2 and 3. *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1375 (Fed. Cir. 2006) ("To anticipate, a prior art reference must place the inventive compound or composition in the possession of the public."). Thus, we find that the

subject matter of Claims 2 and 3 has not been shown to be anticipated by h53AON1.

2.

AZL also argues that the subject matter of the AONs of Claims 2 and 3, as well as that of Claims 38-40 and 42, would have been obvious over VO. We are not persuaded of the obviousness of the subject matter of those claims. As we noted above, it is unpredictable whether exon skipping will be maintained when an AON known to cause exon skipping is modified by changing the sequence length but keeping complementarity. Because of the unpredictability, we are not convinced that one ordinarily skilled in the art would have had a reasonable expectation of success that an AON having the sequence of UWA's SEQ ID NO: 193 would cause exon skipping.

D.

AZL's Motion 1 for a judgment that UWA Claims 1-43 are unpatentable over certain prior art is granted as to Claims 1, 4-37, 41 and 43 and denied as to Claims 2, 3, 38-40 and 42.

VIII.

AZL Motion 2 to deny UWA the benefit of its Australian Application

AZL moves to deny UWA the accorded benefit of the June 28, 2004, filing date of its Australian application AU 2004903474. In AZL's view the Australian application is not a constructive reduction to practice of the subject matter of the count. We grant the motion.

The PTO's Interference Rules define "accord benefit" and "constructive reduction to practice":

> *Accord benefit* means Board recognition that a patent application provides a proper constructive reduction to practice under 35 U.S.C. § 102(g)(1).

> *Constructive reduction to practice* means a described and enabled anticipation under 35 U.S.C. § 102(g)(1), in a patent application of the subject matter of a count.

37 C.F.R. § 41.200. *See Hunt v. Treppschuh*, 523 F.2d1386,1389 (Fed. Circ. 1975). (For the purpose of priority in an interference, where a "parent application is relied upon as a prior constructive reduction to practice[,] . . . the § 112, first paragraph requirements need only be met for an *embodiment* within the count.") *See also*, *Falkner*, 448 F.3d at 1362.

The count of this interference is:

> Claim 15 of [AZL] Application 11/233,495 or Claim 1 of [UWA] Patent 8,455,636.

Declaration, Paper 1, p. 4. The claims of the count are reproduced below:

AZL Claim 15:

> An isolated antisense oligonucleotide of
> [1] 15 to 80 nucleotides comprising
> [a] at least 15 bases of the sequence cuguugccuccgguucug (SEQ ID NO: 29),
> [2] wherein said oligonucleotide induces exon 53 skipping in the human dystrophin pre-mRNA,
> [3] said oligonucleotide comprising a modification selected from the group consisting of:
> [a] 2'-O –methyl,
> [b] 2'-O-methyl- phosphorothioate,
> [c] a morpholine ring,
> [d] a phosphorodiamidate linkage,
> [e] a peptide nucleic acid and
> [f] a locked nucleic acid.

AZL Clean Copy of Claims, Paper 8, 1:3-8.

UWA Claim 1:

> An isolated antisense oligonucleotide of
> [1] 20 to 50 nucleotides in length comprising
> [a] at least 20 consecutive nucleotides of SEQ ID NO:193,

[2] wherein the oligonucleotide specifically hybridizes to an exon 53 target region of the human dystrophin gene inducing exon 53 skipping, and
[3] wherein the uracil bases are optionally thymine bases.

UWA Clean Copy of Claims, Paper 12, APP A-1.

AZL argues that the Australian application neither discloses an AON that is said to cause skipping of exon 53 nor a sequence that meets the limitations of the claims that make up the count. AZL Motion 2, Paper 26, 15:13 – 17:16. UWA does not argue to the contrary. Rather it argues that the motion should not be reached. Since benefit is determined based upon the count and the count may change as a result of the decisions on motion, UWA says that it is premature to reach the motion at this time. UWA Opposition 2, Paper 394, 1:8 – 2:15.

We have reviewed UWA's Australian application and concur with AZL that there is no description of exon 53 skipping or of an AON that would otherwise meet the limitations of the count. The Australian application does not provide any description of exon 53 skipping. That application could not provide a constructive reduction to practice for any count directed to exon 53 skipping that could be formulated.

AZL's Motion 2 to deny UWA the benefit of Australian Application AU 2004903474 is granted. This interference will be redeclared to conform the accored benefit to our decision.

IX.

AZL's Motion 3 for unpatentability under 35 U.S.C. § 101

AZL's Motion 3 requests a judgment that UWA's Claims 1-4, 19-21, and 36-42 are unpatentable under 35 U.S.C. § 101 in view of *Association for Molecular Pathology v. Myriad Genetics, Inc.*, ___ U.S. ____, 133 S.Ct. 2107

(2013). Paper 27. Because those claims cover naturally occurring DNA and are not limited to a new application of exon 53 information, we grant the motion.

UWA's involved claims are directed to AONs of 20-50 nucleobases that hybridizes to a region of exon 53 of the human dystrophin gene causing exon 53 to be skipped. The AON must include at least 20 consecutive nucleobases of UWA's SEQ ID NO: 193. Additionally, the uracil bases may be substituted with thymine. We reproduce representative Claim 1 below (with paragraphing added):

> 1. An isolated antisense oligonucleotide
>
> of 20 to 50 nucleotides in length comprising
> at least 20 consecutive nucleotides of SEQ ID NO:193,
> wherein the oligonucleotide specifically hybridizes to an exon 53 target region of the human dystrophin gene inducing exon 53 skipping, and
> wherein the uracil bases are optionally thymine bases.

UWA Clean Copy of Claims, Paper 8, App A-1, Claim 1.

A.

According to AZL, the Claims 1-4, 19-21 and 36-42 are unpatentable under § 101 because they cover naturally occurring DNA sequences. AZL points out that the DNA version of the AON covered by Claim 1 is identical to sequences present in exon 53 of the dystrophin gene. AZL Motion 3, Paper 27, 5:13 – 6:6.

UWA does not argue that that is incorrect. Rather, UWA argues that the claimed AONs differ in structure, properties, and functionally from anything existing in nature. UWA argues that claimed AONs are a subset of the antisense strand of exon 53 DNA. UWA Opposition 3, 6:6 – 7:13; 7:23 – 9:21. It also argues that each AON will have different binding characteristics. UWA Opposition 3, 6:6 – 7:13.

Myriad effectively answers these points. Myriad's Claim 5 and 6 were directed to a subset of the BRCA1 and BRCA2 DNA—15 or more nucleotides that

encoded the BRCA1 and BRCA2 polypeptides. Those shorter DNA segments were also a subset of the BRCA1 and BRCA2 genes and would necessarily have different properties due to their shorter length. Yet the subject matter of Myriad's Claims 5 and 6 was not considered patent eligible. Myriad, 133 S.Ct. at 2113 and 2118 (discussion of Claim 5 and discussion of isolating DNA). Similar to the situation in *Myriad*, UWA's challenged claims would give it the exclusive right to isolate any strand of 20 to 50 nucleotides that include at least 20 consecutive nucleotides of SEQ ID NO: 193.

We are not persuaded that the cited "functionality" makes any difference as to UWA's claims other than to identify a property of the AONs. A new application of knowledge about exon 53 and its sequence might tip the balance in favor of eligibility. As noted in Myriad:

> It is important to note what is not implicated by this decision.
>
> * * * * *
>
> [T]his case does not involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes. Judge Bryson aptly noted that, "[a]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications.

Myriad, 133 S.Ct. at 2120. None of UWA's challenged claims appear to be limited to the application of exon skipping. In UWA's claims exon skipping defines a characteristic of the AONs, the recitation of that characteristic, however, does not limit the application of the claimed AONs to any particular use or function. The Federal Circuit's holding in *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755 (Fed. Cir. 2014) referred to in UWA's Opposition 3 (Paper 395, 11:17-12:2) is not inconsistent with the Supreme Court's statement quoted above as to claims limited to new applications of the knowledge about the gene (DNA) as compared to claims directed to and

controlling naturally occurring sequences. UWA Claims 1-4, 19-21 and 37-42 have not be shown to have a unique structure, different from anything found in nature. *BRCA1- and BRCA2,* 774 F.3 at 761.

UWA argues that the claims are directed to significantly more than naturally occurring DNA. UWA Opposition 3, 10:1-28. Specifically, UWA argues that the claimed subject matter effects "transformation or reduction of a particular article to a different state or thing." However, none of challenged claims are directed to a method. UWA Claims 1-4, 19-21 and 36-42 do not require that anything be transformed.

Claims 36 and 39-42 are directed to pharmaceutical compositions comprising AONs of Claims 1-3, 19 or 38 and adding a "saline solution including a phosphate buffer" AZL argues that the limitations represent well-understood, routine or conventional additions to pharmaceutical compositions. Such additions are said not to transform a naturally occurring product into a patent eligible application of the AON. UWA Motion 3, Paper 27,

UWA does not challenge this argument. We have reviewed the evidence cited by AZL and agree that the additions are represent well-understood, routine or matters conventional in the art and do not transform Claims 36 and 39-42 into patent eligible subject matter.

AZL's motion for a judgment that UWA's Claims 1-4, 19-21, and 37-42 are unpatentable under 35 U.S.C. § 101 in view of *Myriad* is granted.

X.

AZL Responsive Motion 4 to add two additional claims

AZL moves to add additional claims 104 and 105 in response to UWA's assertions of unpatentability in UWA Motions 1 and 2. Paper 241. We deny the motion. Proposed claim 104 would be unpatentable under 35 U.S.C. § 112 for the same reasons we stated with respect to AZL Claims 15, 76, 78-80, 82, 84, 86, 88-

90, 97, 98, and 100-103. Claim 105 is unnecessary in light of our holding that claim 77 was not proved to be unpatentable.

The two claims suggested by AZL are reproduced below:

> 104. (**New**) An oligonucleotide of between 14 and 50 nucleotides comprising the sequence of h53AON1 (SEQ ID NO: 29), wherein said oligonucleotide comprises a 2'-*O*-methyl-phosphorothioate oligonucleotide modification.
>
> 105. (**New**) An isolated antisense oligonucleotide, wherein the oligonucleotide is 18 nucleotides and comprises the sequence cuguugccuccgguucug (SEQ ID NO: 29), wherein each internal nucleoside linkage of the oligonucleotide is a phosphorothioate linkage.

AZL Motion 4, Paper 241, 1:8-15.

Proposed Claim 104

A party moving to add a claim must show it is patentable. 37 CFR § 41.208(c). We held above that AZL's Claims 15, 76, 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103 were unpatentable under § 112(a). Each of those claims recited a range of nucleobases. We held that those claims were unpatentable because the person having ordinary skill in the art would not have been put in possession of the full range of AON sequence lengths specified in those claims. One of those claims, for example, specified sequence lengths of 18-50 nucleobases. AZL Clean Copy of Claims, Paper 8, Claim 78. The broader scope of "between 14 and 50" nucleobases of proposed claim 104 would be unpatentable for the reasons stated with respect to claims 15, 76, 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103.

Proposed Claim 105

Claim 105 is similar to claim 77substituting phosphorothioate linkage for the Markush group of 2'-*O* –methyl, 2'-*O*-methyl-phosphorothioate, a morpholine ring, a phosphorodiamidate linkage, a peptide nucleic acid and a locked nucleic

acid. Because we held claim 77 was not shown to be unpatentable, we are not persuaded that the amendment is necessary to cure a defect raised by UWA's motions. 37 C.F.R. § 41,121(a)(2). In any event, as an applicant, AZL may seek entry of the amendment when the application returns to the jurisdiction of the patent examiner.

XI.

As a result of the decisions on AZL's Motions 1 and 3 all of Junior Party UWA's claims have been held unpatentable. As UWA has not alleged a date of invention earlier than AZL's accorded benefit date of March 21, 2003, (UWA Priority Statement, Paper 214) there is no apparent reason to continue this interference and proceed to the priority phase. Accordingly, a judgment will be issued in a separate paper.

SUMMARY

We dismiss UWA's Motion 4 to exclude Exhibits 1012, 1067 and 1186 and deny that motion with respect paragraphs 4 to 18 of Exhibit 1125.

We grant UWA's Motion 1 for unpatentability under 35 U.S.C. § 112(a) with respect to AZL Claims 15, 76, 78-80, 82, 84, 86, 88-90, 97, 98, and 100-103, but deny it with respect to AZL Claim 77.

We deny UWA's Motion 2 that AZL's Claims 15, 76-80, 82, 84, 86, 88-90, 97, 98, and 100-103 are indefinite under 35 U.S.C. § 112(b).

We deny UWA's Motion 3 to declare an additional interference.

We grant AZL's Motion 1 that UWA's claims are unpatentable over prior art with respect to Claims 1, 4-38 and 41-43, but deny it as to Claims 2, 3, 38-40, and 42.

We grant AZL's Motion 3 asserting that UWA's Claims 1-4, 19-21 and 37-42 are not directed to patent eligible subject matter under 35 U.S.C. § 101.

We grant AZL's Motion 2 to deny UWA the benefit of the filing date of Australian Application AU 2004903474.

We deny AZL's Motion 4 to add two additional claims to its involved application.

Because all of UWA's claims have been held to be unpatentable, and UWA does not assert a date earlier that AZL's accorded benefit date, there is no apparent reason to proceed to a determination of priority. A judgment will be entered in a separate paper.

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